

**REMARKS**

Claims 1-7 and 12-15 are pending. Claim 12 has been amended to correct a typographical error. No new matter has been added.

**Rejection Under 35 U.S.C. § 103**

The pending claims stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 7,138,405 (“Wyllie”) and U.S. App. No. 09/969,408 (“Sanger”). The Applicants respectfully disagree and request withdrawal of the rejection.

The present invention is directed to pharmaceutical compositions comprising an alpha-adrenoceptor antagonist and a 5-HT<sub>4</sub>-receptor antagonist, as well as methods of using those compositions for the treatment of lower urinary tract symptoms.

Wyllie describes the combination of an alpha-adrenoceptor antagonist and a *muscarinic* antagonist for treatment of lower urinary tract symptoms. Wyllie at col. 3, lines 18-23. It is well known to those of skill in the art that the muscarinic receptor is distinct from the 5-HT<sub>4</sub> receptor. Sanger describes methods for the treatment of bladder hypersensitivity comprising administration of a 5-HT<sub>4</sub> modulator, which may be an agonist or an antagonist. Sanger at ¶ 6. Nowhere in the cited art, or in the knowledge of one skilled in the art, is there any teaching or suggestion that the muscarinic antagonist of the Wyllie composition can be successfully substituted with any of the 5-HT<sub>4</sub> modulators of Sanger to yield a composition useful for the treatment of lower urinary tract symptoms.

The Office supports its allegation of obviousness by stating that “it is well known within the art that muscarinic receptor antagonists often result in the presence of unpleasant side effects (i.e., dry mouth, dry eyes or headache) that may reduce patient compliance. Therefore to increase patient compliance and reduce the possible unwanted side effects, substitution of the 5-HT<sub>4</sub>-receptor antagonist for the muscarinic antagonist would have been obvious to do and likely profitable.” Action at 7-8. This statement is wholly unsupported and is insufficient to provide the requisite teaching, suggestion, or motivation necessary to support a *prima facie* case of obviousness. M.P.E.P. § 2144.03(A); *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1731 (2007). “Official notice unsupported by documentary evidence should only be taken by the examiner where the facts asserted to be well-known, or to be common knowledge in the art are capable of instant and unquestionable demonstration as

being well-known. . . It would ***not*** be appropriate for the examiner to take official notice of facts without citing a prior art reference where the facts asserted to be well known are not capable of instant and unquestionable demonstration as being well-known. For example, assertions of technical facts in the areas of esoteric technology or specific knowledge of the prior art must always be supported by citation to some reference work recognized as standard in the pertinent art.” M.P.E.P. § 2144.03(A) (emphasis in original).

In addition, because of the differences in biological activity between the muscarinic receptor and the 5-HT<sub>4</sub> receptor, one of skill in the art would not have been able to predict whether the substitution of a 5-HT<sub>4</sub> antagonist for the muscarinic antagonist of Wyllie would have produced a ***predictable, successful*** result. M.P.E.P. § 2143.02. The Office cites no suggestion or teaching that would suggest the two therapeutic agents are interchangeable. Moreover, the standard for obviousness is not whether the substitution would have been “profitable,” as the Office states, but whether it would have yielded a predictable, successful result. M.P.E.P. § 2143.02.

The Office also cites that “[i]t is however, *prima facie* obvious to combine two compositions taught in the prior art useful for the same purpose, in order to form a third composition to be used for the very same purpose.” Action at 8 (citing *In re Kerkhoven*, 626 F.2d 846, 850 (CCPA 1980)). *Kerkhoven* is inapplicable here. The invention in *Kerkhoven* was a detergent, not a pharmaceutical intended to be administered to a patient in need of treatment. Combining different drug compositions for use in treating a patient encompasses factors and an unpredictability that cannot be equated with combining detergent compositions in the obviousness context.

### **Conclusion**

The Applicants assert that a *prima facie* case of obviousness has not been established and that the pending claims are patentable over the cited art. A Notice of Allowance is, therefore, earnestly solicited. If the Examiner believes discussion would expedite the allowance of the claims, the Examiner is invited to call the undersigned at (215) 564-8918.

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